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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/558,741	04/26/2000	James S. Huston	PP0926.105	1163

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EXAMINER
HELMS, LARRY RONALD

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/558,741	Applicant(s) HUSTON ET AL.	
	Examiner Larry R. Helms	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *33 and 97-100* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33 and 97-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicants amendments have obviated the restriction requirement of 3/27/01, paper #11.

2. Claims 42, 43, and 50-96 have been canceled.

Claim 33 has been amended and claims 97-100 have been added.

3. Claims 97-100 are pending and under examination.

Petition

4. The petition filed under 37 CFR 1.48(b) for the removal of inventors Lou L. Houston and David B. Ring has been accepted.

Information Disclosure Statement

5. The IDS filed 5/30/00 has been partially considured with respect to all U. S. Patents, however, all other documents have not been considured because the cited references were not in 08/462,641. The IDS has been placed in the file and if Applicants would supply a copy of the references, they will be considured at that time.

Specification

6. The disclosure is objected to because of the following informalities:

a. The first line of the specification should be updated to indicate the correct lineage to related applications. The amendment filed 10/01/01 has not been entered as

it related to the Cross reference to the related applications. The amendment filed 4/26/00 as paper # 1 requested the deletion of lines 7-9 on page 1 and as such this line is not found on page 1 and as such the added material could not be entered. It is unclear what applications the instant application claims benefit from.

b. The attempt to incorporate subject matter into this application by reference to sections in U.S. Patent 5,091,513 and to Figures 1a and 2A-D (now figures 7 and 8A-D) is improper because to incorporate material by reference, the host document / application must identify with detailed particularity what specific material it incorporates and clearly indicate where the material is found in the various documents. See Advanced Display Systems, Inc. v. Kent State Univ., 54 USPQ2d 1673 (Fed. Cir. 2000) citing In re Seversky, 177 USPQ 144, 146 (CCPa 1973). On page 26 of the instant application the specification recites "A detailed description for engineering and producing sFv proteins by recombinant means appears in US Patent 5,091,513", however, the material added by the amendment of 10/01/01 contains the summary of the invention as well as descriptions of terms and what other regions the BABS can comprise such as fusion proteins and hinge regions (column 11-12) as well as the advantages of BABS (see column 7-8 of 5,091513). Also Figure 1A and 2A-D do not relate to sFv, they relate to fusion proteins and Fv and VH fusion proteins. In addition, the response filed 10/01/01 was not accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA

1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Appropriate correction is required.

Claim Objections

7. Claim 33 and 100 are objected to because of the following informalities:

a. Claim 33 is objected to because of the following informalities: Claim 33 contains an apparent typographical error in the phrase "linked a polypeptide linker". The phrase should recite "linked to a polypeptide linker".

b. Claim 100 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 98. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 34-100 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 33-100 are indefinite for reciting "variable domain independently sequence comprising" in claim 33 because the exact meaning of the phrase is not clear. Does the phrase mean each domain is a separate amino acid sequence or each domain is "independently sequenced"?

b. Claims 97-100 are indefinite for reciting "derived from human immunoglobulin sequences" *because the exact meaning of the phrase is not clear.* The term "derived" is not one which has a universally accepted meaning in the art nor is it one which has been adequately defined in the specification. The primary deficiency in the use of this phrase is the absence of a ascertainable meaning for said phrase. Since it is unclear how the framework regions or the CDRs are to be derivatized to yield the class of derivatives referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of compounds to said phrase. Further, it is not clear whether the framework or CDRs are "derived" by attachment of a detectable marker, therapeutic molecule, some other molecule or altering the amino acid sequence, for examples. In addition, since the term "derived" does not appear to be clearly defined in the specification, and the term can encompass proteins with amino acid substitutions, insertions, or deletions, antibody fragments, chemically derivatized molecules, or even antibody mimetics. In absence of a single defined art recognized

meaning for the phrase and lacking a definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claims.

c. Claims 98 and 100 are indefinite for reciting "wherein at some of said complementarity determining regions are[a] derived from human immunoglobulin sequences" because the exact meaning of the phrase is unclear. Does the phrase mean the CDRs are from human immunoglobulin or are some of the CDRs from a human immunoglobulin or some other meaning?

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 33 and 97-100 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Newly amended claim 33 and newly added claims 97-100 recite limitations of a polypeptide comprising two variable domains each comprising three CDRs and FR wherein each variable domain is linked to a polypeptide linker to form a single polypeptide chain and the regions together define a variable region binding domain inmmunologically reactive with an antigen and a third amino acid sequence being part of the single polypeptide chain having a biological activity independent of the

immunologically reactivity, wherein the FRs are from human immunoglobulin and the variable domains are from human immunoglobulins.

The response filed 10/01/01 did not state where support for the amendment or the newly submitted claims can be found in the specification as originally filed. The specification as well as application 08/575724 (now U.S. Patent 6,207804) and 07/831967 (refilled as 08/356786, now U.S. Patent 5,877,305), which the instant application claims benefit from does not support the limitation "single polypeptide chain" or "independently sequence" or "derived from human immunoglobulin sequences" or "at some of said complementarity regions". In addition, the specification does not seem to support the generic language of any linking polypeptide in any orientation of the variable domains and CDRs from human immunoglobulin sequences. Applicant is required to provide support for all limitations in the claims in the specification as originally filed or remove them from the claims.

12. Claims 98 and 100 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence

or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a polypeptide wherein some of the CDR regions are from human immunoglobulin sequences. The specification teaches humanization of a single-chain Fv which contains murine CDRs and human FR sequences (see page 35-36. The specification does not enable some CDR regions from human immunoglobulin sequences.

The claims are not commensurate in scope with the enablement provided in the specification. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced

by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that the polypeptide as defined by the claims which may contain alterations in the CDRs wherein some of the CDR regions are human, have the required binding function. The specification provides no direction or guidance regarding how to produce polypeptides as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Further, the specification does not teach that a functional binding polypeptide can be obtained by replacing some of the CDR with those from a human immunoglobulin.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 33 and 97, 99 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 and 9-12 of U.S. Patent No. 5,091,513 (IDS #3) in view of Jones et al (Nature 321:522, 1986).

The claims have been described supra.

The claims in U.S. Patent 5,091,513 are drawn to single chain polypeptides comprising a third amino acid sequence that has a binding activity independent of the single chain polypeptide. U.S Patent 5,091,513 does not teach framework regions from a human immunoglobulin. This deficiency is made up for in the teaching of Jones.

Jones et al teach replacement of the CDRs of human antibody with those from a mouse (see entire document).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used FR from a human immunoglobulin and CDRs from a mouse antibody as taught by Jones in the single chain polypeptides of Huston et al (5,091,513).

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used FR from a human immunoglobulin and CDRs from a mouse antibody as taught by Jones in the single chain polypeptides of Huston et al (5,091,513) because Jones et al teach variable domains made by grafting mouse CDRs into human FRs could have therapeutic potential (see page 525).

Thus, it would have been obvious to humanize the single chain polypeptides of Huston et al with the method of Jones for therapeutic potential in humans.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 33 and 97 and 99 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klausner (BioTechnology 4:1041 and 1043, 12/86) and further in view of Pastan et al (Cell 47:641-648, 12/86) and Jones et al (Nature 321:522-525, 5/1986).

The claims recite of a polypeptide comprising two variable domains each comprising three CDRs and FR wherein each variable domain is linked to a polypeptide linker to form a single polypeptide chain and the regions together define a variable region binding domain inmmunologically reactive with an antigen and a third amino acid sequence being part of the single polypeptide chain having a biological activity independent of the immunologically reactivity, wherein the FRs are from human immunoglobulin and the variable domains are from human immunoglobulins.

Klausner teach single chain antibodies which comprise a heavy chain and a light chain connected by a polypeptide linker. Klausner does not teach a third polypeptide being part of the single polypeptide chain or a human framework region. These deficiencies are made up for in the teachings of Pastan et al and Jones et al.

Pastan et al teach immunotoxins comprising an antibody and a toxin.

Jones et al teach humanization of antibodies which comprise mouse CDRs and human FR.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced an immunotoxin comprising a single chain antibody as taught by Klausner and a toxin as taught by Pastan et al and humanize it as taught by Jones et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced an immunotoxin comprising a single chain antibody as taught by Klausner and a toxin as taught by Pastan et al and humanize it as taught by Jones et al because Klausner teach "Single-chain molecules are also easier to purify" (see page 1043) and "eventually the scientists will address therapeutics that take advantage of an antibodies binding fragment attached to an anti-cancer agent" (see page 1043). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced an immunotoxin comprising a single chain antibody as taught by Klausner and a toxin as taught by Pastan et al and humanize it as taught by Jones et al because Pastan et al teach that immunotoxins are effective for cancer therapy. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced an immunotoxin comprising a single chain antibody as taught by Klausner and a toxin as taught by Pastan et al and humanize it as taught by Jones et al because Jones teach variable domains made by grafting mouse CDRs into human FRs could have therapeutic potential (see page 525).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

19. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

Sheela D. Huff
SHEELA HUFF
PRIMARY EXAMINER